

Review

New Cosmetic Contact Allergens

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Abstract: Allergic and photo-allergic contact dermatitis, and immunologic contact urticaria are potential immune-mediated adverse effects from cosmetics. Fragrance components and preservatives are certainly the most frequently observed allergens; however, all ingredients must be considered when investigating for contact allergy.

Keywords: allergic contact dermatitis; contact urticaria; cosmetics; fragrances; preservatives

1. Introduction

Cosmetics may cause both delayed-type allergic reactions, expressed as contact or photo-contact dermatitis, and immediate-type allergic reactions, *i.e.*, the contact urticaria syndrome, which includes cutaneous and also extra-cutaneous symptoms, such as conjunctivitis, respiratory problems, or even anaphylaxis.

Among the most important culprits are fragrances and preservative agents, but reactions also occur to category-specific products such as hair dyes, nail cosmetics, sunscreens, as well as to various ingredients such as antioxidants, vehicle components, and emulsifiers (see [1] for a review). Reactions to natural products are, in general, very complex. In fact, all cosmetic ingredients may induce sensitization and the literature continuously reports on new allergens, which will be focused on here.

2. The Allergens

Fragrance components are important cosmetic allergens. In the baseline series tested in patients with suspected allergic contact dermatitis, the following markers for detection of fragrance allergy are included: Fragrance mix, which contains eight perfume components (amyl cinnamal, cinnamal, cinnamyl alcohol, hydroxycitronellal, eugenol, isoeugenol, geraniol, and *Evernia prunastri* (oakmoss)

extract), and Fragrance mix II, which contains six components (hydroxyisohexyl 3-cyclohexene carboxaldehyde, farnesol, citral, citronellol, coumarin, and alfa-hexyl cinnamal), as well as hydroxyisohexyl 3-cyclohexene carboxaldehyde separately in a higher (5%) concentration than in the mix (2.5%). They remain good screening agents for contact allergy to perfumes [2]. However, to diagnose, there is still the need to test with other fragrance materials, among which 26 fragrance components that since March 2005 are labeled as cosmetic ingredients on the packaging (Annex 3 of the Cosmetic Directive 2003/15/EC) [3], but also the patient's own products, additional perfume mixtures such as essential oils, that together with other fragrance components are recognized as contact allergens, and which should be labeled and tested as well [4]. In this context also flavoring agents (e.g., in toothpaste or lip cosmetics), such as carvone [5] and menthoxypropanediol [6] should be taken into account.

It is interesting to mention that certain substances are not allergenic per se, the typical examples being terpenes, such as limonene and linalool, which behave as prehaptenes giving rise to sensitizing air-oxidation products that are widely used in consumer (cosmetic, household, industrial) products and recognized as important sensitizers [7,8]. Moreover, some haptens require metabolic activation in the skin, called prohaptens [9]. This sometimes explains concomitant reactions observed between chemically and metabolically related fragrance ingredients; for example, a recent study explored the relationship between contact allergies to geraniol and citral and found that geranial, an autoxidation product and skin metabolite of geraniol, is the main sensitizer in the mixture citral and thus responsible for concomitant reactions between them [10].

Fragrance-allergic patients do indeed often present with multiple positive patch-test reactions, which may be due to concomitant or subsequent sensitization, the presence of common or cross-reacting ingredients that are present in other natural products as well (see below), and even certain contaminants; for example, resin acids and their oxidation products, being the main allergens in colophonium, have been identified in *Evernia prunastri* (oak moss) due to contamination with *Evernia furfuracea* (tree moss) that is sometimes used a substitute for the more expensive oak moss [2].

Preservatives have become among the most important cosmetic allergens, for which shifts have occurred over the years [11]. In recent years, cosmetic products have created a worldwide epidemic of contact-allergic reactions due to the presence of methylisothiazolinone (MI), in particular, both in leave-on and also rinse-off products [12,13]. MI is a weaker sensitizer than the chlorinated derivative methylchloroisothiazolinone (MCI), but also less efficient as a preservative, hence larger use concentrations (up to 100 ppm) than the mixture MCI/MI (max. 15 ppm) are admitted. Initially, most cases were due to the use of wet wipes (moist toilet paper) for intimate hygiene (also for babies causing hand dermatitis in their parents, Figure 1), but later on facial skin-care products, body lotions, deodorants, and even rinse-off products (shampoos, liquid soaps) turned out to be important sensitization sources (e.g., [14]). MI is sometimes responsible for severe skin lesions and atypical clinical symptoms, leading to a delay in the correct diagnosis (e.g., [14,15]), and respiratory problems may occur as well. Moreover, regarding the frequency of positive reactions observed, the studies carried out have even underestimated the true MI-epidemic given the fact that patch tests were not always conducted with the most optimal test concentrations. Indeed, in order to correctly diagnose contact allergy caused by MCI and MI it is of utmost importance to include in the European baseline

series MCI/MI 200 ppm (instead of 100 ppm) and preferably 2000 ppm instead of MI 200 or 500 ppm (as previously tested), using a micropipette for application [16,17].



Figure 1. Severe hand dermatitis from baby wipes in a parent.

The cosmetic industry already advised its members to phase out the use of MI in leave-on products and the European authorities should urgently regulate this, as is the case for the presently allowed mixture of MCI/MI (Official Journal of the European Union 26.9.2014, L281/1-4. Commission Regulation (EU) No 1003/2014 of 18 September 2014 amending Annex V to Regulation (EC) No. 1223/2009 of the European Parliament and of the Council on cosmetic products). Indeed, from 16 July 2015 only cosmetic products which comply with this regulation shall be placed, and from 16 April 2016 be made available, on the Union market, respectively. Moreover, household (cleansing products) and industrial products, such as paints should be regulated as well since they are also important sensitization and elicitation sources, the latter being responsible for severe airborne dermatitis (and also systemic symptoms).

Recently, polyhexamethylene biguanide (synonyme polyaminopropyl biguanide, polyhexanide), a widely used hospital disinfectant and antiseptic has shown to be another potential cosmetic allergen in wet wipes (and facial make-up cleansers, Olivier Aerts, personal communication), inducing both delayed-type eczematous [18], but also severe immediate-type reactions, expressed as the contact urticaria syndrome [19,20].

Among the antioxidants, the number of contact-allergic reactions to propyl gallate that may cross-react with other gallates, also used as food additives, seems to have increased over the years [21], which may be attributed to an increased use in cosmetics concomitant to a reduced use in food, with oral tolerance reactions less likely to develop. Sulfites and bisulfites have shown to be relevant allergens in cosmetic creams and hair dyes [22]. Some antioxidants are used more specifically in sunscreen and also anti-aging products; examples are vitamin C derivatives such as ascorbyl tetraisopalmitate [23,24] and vitamin C ethyl [25], and idebenone or hydroxydecyl ubiquinone (a synthetic analog of Coenzyme

Q10 (CoQ10) [26]. Furthermore, we observed 6 cases of contact allergy to tetrahydroxypropyl ethylenediamine, a chelating agent, due to its presence in skin care products; no cross-reactions to ethylenediamine or edetate were observed [27].

With regard to category-specific ingredients, with oxidative-type hair dyes, allergens other than para-phenylene diamine (PPD) are also concerned (e.g., [28]), both in hairdressers and clients. PPD is even used for dyeing eyelashes and causes severe contact dermatitis and blepharoconjunctivitis [29,30]; this practice should be forbidden by EU legislation. Beside severe cases of contact dermatitis, immediate-type reactions or the contact-urticaria syndrome (even anaphylaxis) may also occur, and not only due to PPD [31], but also to direct hair dyes, such as basic blue 99 and basic brown 17 [32]. This is also the case with hair-bleaching agents based on persulfates [33] that have been recognized as such for several decades.

Recently, phenylethyl resorcinol, a skin-lightening agent, was reported to be a new cosmetic allergen as well [34].

As to nail cosmetics, formaldehyde is a potential allergen in nail hardeners, while acrylates and methacrylates have, during the last decade, become important causes of reactions to nail gel formulations, in particular, in clients but particularly in manicurists [35].

Sunscreens are increasingly being used, not only in sunscreen products (also in children), but in “anti-aging” and day-care products as well. They are also used to prevent degradation by sunlight exposure, hence a potential allergen in all product types including fragrances and hair-care products [36]. Sunscreen agents may be responsible for allergic and photo-allergic reactions, and also immediate-type reactions, e.g., benzophenone-3 (see [37] for a review). Contact- and photo-contact allergy to octocrylene that also stabilizes other sunscreens such as butyl methoxydibenzoylmethane, has been recently extensively reviewed [38]. Its relation to simultaneous sensitivity to the fragrance component cinnamyl alcohol, as well as to photosensitivity to ketoprofen, a non-steroidal anti-inflammatory drug used to treat muscle pain, needs to be further elucidated, since the chemical relationship, as in the case for benzophenones that clearly cross-react with ketoprofen [39], is not obvious. Recently polysilicone-15 has been reported as the cause of allergic contact cheilitis in a lip care balm [40]. A European photo-patch test series covering the most important photo-allergens has been proposed [41].

A large number of newer emulsifiers, emollients, or excipients have been reported as cosmetic allergens [1], including esters which are not known to be reactive chemicals, hence, not notable contact allergens (but sometimes used in rather high concentrations). Examples of the most recent ones described are emollients and skin conditioning agents, *i.e.*, cetearyl isononanoate [42], a compound closely related to other isononanoates [43], neopentanoates and hexanoates, within which cross reactions may occur (Figure 2), and ditrimethylolpropane triethylhexanoate [44]. Other examples of newly reported allergens are glyceryl (mono) caprylate [45], triceteareth-4-phosphate [46], and methylglucose dioleate [47], as well as distearyl phtalic acid amide, the latter as a cause of shampoo dermatitis [48].

Contact allergy to ethylhexylglycerin (synonyme: octoxyglycerin), another widely-used skin conditioning agent, has been reported several times in the literature, the most recent case concerning its presence in sunscreens [49]. Recently, two cases of contact allergy to capryloyl salicylic acid were described as well [50].

Alkyl glucosides, such as coco and lauryl glucosides, emulsifiers and mild surfactants, and decyl glucoside that is associated with the sunscreen agent Methylene Bis-Benzotriazolyl Tetramethylbutyl-phenol, have been repeatedly reported as cosmetic allergens as well (see [51] for a review). Another mild surfactant reported is sodium cocoamphopropionate [52] that is closely related to sodium cocoamphoacetate [53].



Figure 2. Cross reactions between isononyl isononanoate (synonyme 3,5,5-Trimethylhexyl 3,5,5-trimethylhexanoate) and other related hexanoates and neopentanoates, widely used emollients and skin-conditioning agents.

Humectants such as butylene-, pentylene-, and hexylene-glycol, *i.e.*, aliphatic alcohols with similar uses (solvent, humectant and antibacterial) to propylene glycol that is considered to be more irritant and allergenic, have become very popular in recent years. They sometimes cross-react with each other and may also cause immediate-type reactions [54].

Copolymers are also potential allergens (see [55] for a review), although the allergenic culprits in them have not been identified. The latest reports concerned C30–38 olefin/isopropyl maleate/Ma copolymer as an allergen in a sunscreen product [56] and also a moisturizer [57].

Examples of natural ingredients, such as plant extracts or other natural substances [58,59] having caused contact allergy are: Glycyrrhetic acid and castor oil [60], argan oil [61,62], carnauba [63] and candelilla [64] inducing cheilitis, chondroitine sulfate [65] and other oligosaccharide derivatives [66]. There are, however, several problems involved regarding the allergenic behaviour of natural products: These are complex mixtures of many chemical ingredients, the exact nature of which is, in most cases, not known; their chemical nature, hence, their allergenic potency may vary from batch to batch according to their origin, which also influences patch testing since standardization is not possible; moreover, there is the role of autoxidation, skin penetration, and/or skin metabolism [9].

Multiple positive reactions to different natural products may be observed in sensitized patients. For example, patients reacting to plant species from the *Compositae* or *Asteraceae* family are frequently positive to fragrance ingredients and also colophonium [67], which is caused by the common presence of air-oxidized terpene compounds. This broadens, of course, the spectrum of sensitization sources to which the allergic subject is being exposed. Moreover, cosmetic labelling of plant products leads to confusion, not only because their INCI names are in Latin, hence not easily understandable by most

consumers, but sometimes, they are used because of other properties than being fragrances, and as such even in “non-scented” products [68].

Nowadays, skin-care products, especially in those intended to treat dry skin in atopic subjects (often children) often contain potentially sensitizing protein-containing plant extracts (e.g., from soybean, oat, wheat) or hydrolyzed proteins, in particular, which may, beside delayed-type reactions, also cause IgE-mediated contact urticaria [69]. Recently, a 3-year old atopic boy was described who had probably been sensitized via maternal skin contact (by proxy) to hydrolyzed wheat protein contained in a moisturizer [70]. With regard to percutaneous sensitization, high molecular weight wheat hydrolysates seem to be more allergenic than the lower ones [71]. The use of hydrolyzed proteins has, however, given rise to controversies [72,73] since subjects may get sensitized through topical preparations and subsequently develop food allergies (e.g., [69]).

3. Conclusions

Allergic and photo-allergic contact dermatitis, and immunologic contact urticaria are potential immune-mediated adverse effects from cosmetics, with so-called “hypo-allergenic” products being not necessarily less sensitizing [74]. Fragrance components and preservatives are certainly the most frequently observed allergens, however, all ingredients must be considered when investigating for contact allergy.

Once the diagnosis has been made by testing with all ingredients of the product suspected to be the cause of the dermatitis, and for which patch-test concentrations and vehicles can be searched for [75], sensitized subjects should be able to avoid contact with the allergenic culprits. In our department, since many years we have distributed lists of cosmetic products not containing the respective allergen(s) and that can be used as safe alternatives [76], but an “Allergyapp” might be a solution for the future as well [77].

Conflicts of Interest

The author declares no conflict of interest.

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